Inflammation and the etiology of type 2 diabetes

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Summary

Type 2 diabetes is increasingly common worldwide and is beginning to strike younger age groups. Almost 90% of all patients with diabetes show insulin resistance, which also precedes the first symptoms of diabetes. The mechanisms underlying the development of insulin resistance are not well understood. In recent years, several studies have been published that implicate subclinical chronic inflammation as an important pathogenetic factor in the development of insulin resistance and type 2 diabetes. This opens new perspectives for diagnosis and treatment of early insulin resistance and incipient glucose intolerance.

Surrogate markers for this low-grade chronic inflammation include CRP, IL-6 and TNF-α. Some antidiabetic agents, for example, glitazones that reduce insulin resistance, and insulin itself, reduce inflammation. Conversely, antiinflammatory drugs (ASA/NSAID) may improve glucose tolerance. Vasoactive drugs that are often prescribed to people with diabetes, for example, statins and ACE inhibitors/angiotensin receptor antagonists, also counteract inflammation and reduce the risk of type 2 diabetes. More specific and sensitive biomarkers should be identified, which may predict early disturbances in insulin sensitivity and cardiovascular risk. Also, inflammatory signalling pathways need to be explored in greater detail, and may form the basis of drugable targets against the epidemic of insulin resistance and atherosclerosis. Copyright © 2005 John Wiley & Sons, Ltd.

Introduction

Type 2 diabetes is increasing worldwide and is seen in ever-younger age groups [1,2]. We can expect this to lead to momentous public health problems, especially in the form of premature cardiovascular morbidity. Nearly 90% of all patients with type 2 diabetes show insulin resistance, which usually also precedes the first symptoms of the disease [1,2]. Insulin resistance is one component of metabolic syndrome X, which also includes hypertension, obesity, dyslipidemia, endothelial dysfunction (as shown by e.g. microalbuminuria) and inhibited fibrilosis, leading to a prothrombotic state [3–5]. The exact mechanisms underlying the development of insulin resistance are poorly understood; no genetic aberrations that explain the phenomenon have been identified except in anecdotal cases.

In terms of quantity, the most important complications of type 2 diabetes are macroangiopathies, that is, myocardial infarction and stroke, which cause 70% of the deaths related to type 2 diabetes [1,3–5]. In contrast to microangiopathies (e.g. nephropathy and retinopathy), where the causal relation to hyperglycemia is well supported, the link between hyperglycemia and macroangiopathy is uncertain, at least in terms of the possibility of reducing macrovascular morbidity solely by reducing hyperglycemia [3–5].
In recent years, several studies have been published suggesting that subclinical chronic inflammation might be an important pathogenetic factor in the development of insulin resistance and type 2 diabetes [3–14]. This opens new perspectives on both diagnosis and treatment of incipient insulin resistance and glucose intolerance.

**Epidemiological studies**

Type 2 diabetes and obesity are both important risk factors for development of premature atherosclerosis and ischemic heart disease. Both conditions are also associated with inflammatory processes in the endothelium and oxidative stress. Many population-based studies show strong co-variation between inflammatory markers and perturbed carbohydrate and lipid metabolism, obesity and atherosclerosis [15–20]. Plasma levels of high-sensitivity C-reactive protein (hsCRP) serve as an independent predictor of future cardiovascular risks, even in healthy subjects. Adjusting for obesity partly weakens the correlation, but does not eliminate it. Given this observation, post-hoc analyses of data from the West of Scotland Coronary Prevention Study (WOSCOPS) cohort of middle-aged men were carried out, to assess C-reactive protein (CRP) as a risk factor for development of diabetes. Such a correlation was found; moreover, it was independent of other established risk factors [18].

The effect of the inflammatory activity was also dose-dependent; for instance, CRP in the upper quintile was associated with a more than threefold increased risk of diabetes, even after adjustment for all the other variables.

Inflammation is thus associated with reduced insulin sensitivity, and from a teleological viewpoint, this is probably advantageous for the organism, at least in the early stages of an infection. Insulin resistance in insulin-sensitive tissue would increase the availability of substrate for the immune system, whose glucose uptake is not regulated by insulin. However, if this system is constantly activated, long-lasting insulin resistance can result in development of type 2 diabetes.

It has been suggested that type 2 diabetes is the final result of an acute phase reaction during which cytokines are released in large amounts from adipose tissue [21], as well as from macrophages recruited into adipose tissue, sustaining inflammation and impaired adipocyte function [22]. This process, driven by excess energy intake, is regulated by genetic factors. According to this hypothesis (schematically illustrated in Figure 1), a variety of cytokines (particularly interleukin 1 [IL-1], interleukin 6 [IL-6] and tumor necrosis factor α [TNF-α]) act on the liver to increase production of, for example, VLDL lipoproteins, which causes the characteristic diabetic dyslipidemia. Likewise, these cytokines stimulate hepatic production of atherosclerotic risk factors such as fibrinogen; they also stimulate release of leptin from adipose tissue and may possibly increase secretion of ACTH in the CNS. The latter, alongside the direct effects of cytokines on the adrenal glands, leads to increased cortisol production, which can contribute to hypertension, obesity and insulin resistance [23]. In obese subjects, there is also an increased metabolic clearance of glucocorticoids; this can have the secondary effect of activating the cortisol axis [23]. It is still a matter of debate whether the cytokines directly influence insulin-producing beta cells in humans over the long term [24]. Cytokines, when given to humans or animals, induce insulin resistance and hypertriglyceridemia [21]. A few attempts have been made to block inflammation acutely, in humans, using TNF-α antagonists, but have not resulted in any measurable improvement of metabolic state [25]. This illustrates the complexity of the system, and may imply that the effects of a brief blockade of inflammation will quickly be reversed by the chronic inflammatory conditions.

Cytokines can also exert pro-thrombotic effects on endothelial cells and directly increase capillary permeability (which manifests itself as microalbuminuria in patients with diabetes). Cytokines produced locally, for instance, in the inflamed plaques so frequently seen in patients whose diabetes is not well controlled, may cause oxidative stress and endothelial dysfunction, and hence further aggravate the atherosclerotic process [5]. It has also been shown that the serum levels of CRP, IL-6, fibrinogen, PAI-1 (plasminogen activator inhibitor 1), amyloid A and sialic acid are increased in patients with type 2 diabetes, and that the magnitude of the increase correlates with the degree of hyperglycemia [3–10,20,21]. If this hypothesis is correct, it may have consequences for treatment: drugs that inhibit the acute phase reaction and the ensuing inflammation could potentially increase insulin sensitivity and retard the development of diabetes.

Obesity-mediated cytokine release is probably pivotal in increasing the systemic levels of CRP and IL-6. Both IL-6 and TNF-α increase hepatic synthesis of CRP [5]. This could explain the reduction in insulin resistance that accompanies weight loss. Likewise, the degree of inflammation goes down when physical activity goes up and energy intake is restricted [5]. Even though obesity, measured as high body mass index (BMI) and/or waist-hip circumference ratio, entails increased production of CRP and IL-6, multivariate analysis shows the levels of the cytokines to be high even after adjustment for obesity [5]. Smoking has recently emerged as a risk factor for type 2 diabetes, and intriguingly, smokers show elevated levels of inflammatory markers in serum, probably due to pro-inflammatory substances in cigarette smoke or low-grade inflammation in airway epithelium [5].

**Results of treatment trials**

For a summary, see Table 1.
Figure 1. Connections between life style, insulin resistance, inflammation and atherosclerosis. This schematic figure shows the proposed connections between life style factors, insulin resistance, inflammation and atherosclerosis. For further details, see text.

ACE inhibitors

The CAPP study (Captopril Prevention Project) was the first controlled trial to show that a drug that interferes with the renin-angiotensin system (RAS), namely, the angiotensin converting enzyme (ACE) inhibitor captopril, reduces the risk of developing type 2 diabetes among patients with hypertension [26]. The study was designed to compare the effects of captopril and conventional antihypertensive therapy (beta blockers, diuretics or both) on cardiovascular morbidity and mortality. The relative proportion of patients with newly diagnosed type 2 diabetes was 11% lower in the captopril group than in those who received conventional therapy.

These results were later confirmed in the HOPE study (Heart Outcomes Prevention Evaluation), in which a fixed dose of the ACE inhibitor ramipril (10 mg/day) was given either as monotherapy or in addition to conventional treatment with beta blockers, diuretics and calcium antagonists [27]. It is important to note that both treatment arms included the same proportion of patients taking beta blockers, 39%. This greatly facilitates

Table 1. Results of treatment trials where reduced risk of diabetes development has been seen

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>No. of patients</th>
<th>Patient group, disease, age, sex</th>
<th>Active treatment</th>
<th>Control treatment</th>
<th>Effect measure</th>
<th>Risk (treated group)</th>
<th>Risk (control group)</th>
<th>Absolute risk reduction (%)</th>
<th>Relative risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPP (26)</td>
<td>10985</td>
<td>Diastolic hypertension men and women 25–66 yrs</td>
<td>Captopril</td>
<td>Beta blocker, diuretics</td>
<td>Incident diabetes</td>
<td>6.13</td>
<td>6.92</td>
<td>0.79</td>
<td>11</td>
</tr>
<tr>
<td>HOPE (27)</td>
<td>9297</td>
<td>Cardiovascular disease, men and women &gt; 55 yrs</td>
<td>Enalapril</td>
<td>Placebo</td>
<td>Incident diabetes</td>
<td>3.6</td>
<td>5.4</td>
<td>1.8</td>
<td>33</td>
</tr>
<tr>
<td>SOLVD (28)</td>
<td>291</td>
<td>Left ventricle dysfunction, men and women 18–80 yrs</td>
<td>Losartan</td>
<td>Placebo</td>
<td>Incident diabetes</td>
<td>5.9</td>
<td>22.4</td>
<td>1.65</td>
<td>74</td>
</tr>
<tr>
<td>LIFE (29)</td>
<td>7998</td>
<td>Hypertension and left ventricular hypertrophy, men and women 55–80 yrs</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>Incident diabetes</td>
<td>6.0</td>
<td>8.0</td>
<td>2.0</td>
<td>25</td>
</tr>
<tr>
<td>CHARM (31)</td>
<td>3023</td>
<td>Heart failure grade II-IV, men and women &gt; 18 yrs</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>Incident diabetes</td>
<td>3.1</td>
<td>5.1</td>
<td>2.0</td>
<td>39</td>
</tr>
<tr>
<td>WOSCOPS (18)</td>
<td>5974</td>
<td>Healthy subjects with hypercholesterolemia, men 45–64 yrs</td>
<td>Pravastatin</td>
<td>Placebo</td>
<td>Incident diabetes</td>
<td>1.90</td>
<td>2.76</td>
<td>0.86</td>
<td>30</td>
</tr>
<tr>
<td>ALPINE (32)</td>
<td>392</td>
<td>Patients with newly detected hypertension, mostly women 18–75 yrs</td>
<td>Candesartan</td>
<td>Hydrochlorothiazide</td>
<td>Incident diabetes</td>
<td>0.5</td>
<td>4.1</td>
<td>3.6</td>
<td>88</td>
</tr>
</tbody>
</table>

\*post-hoc analysis.
interpretation of the results, as several epidemiological studies have shown that for patients with high blood pressure, treatment with beta blockers is a significant risk factor for development of type 2 diabetes [27]. Over the four to five years when the HOPE study was ongoing, treatment with ramipril gave a 33% reduction of the relative risk of developing type 2 diabetes [27].

A retrospective analysis of data from SOLVD (Studies of Left Ventricular Dysfunction) revealed that enalapril had similar effects for patients with left ventricular dysfunction [28]. On an average, the study period was 2.9 years. The study showed that 5.9% of the patients taking enalapril developed diabetes during the study period, as compared to 22.4% of those taking placebo, giving a relative risk reduction of an entire 74%.

**Angiotensin receptor antagonists**

The recently published LIFE study (Losartan Intervention For Endpoint reduction in hypertension) showed that losartan reduced the relative risk of developing type 2 diabetes by 25% compared to the beta blocker atenolol [29]. However, the study included no placebo-treated control group. It is therefore likely that the reduction of incident diabetes reflects the net result of both increased insulin sensitivity in the group taking losartan and increased insulin resistance in the group taking atenolol.

Similar findings were just reported in studies focused on another angiotensin receptor antagonist, namely, candesartan [30,31]. These CHARMS studies (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), unlike LIFE, are placebo-controlled. In CHARM-Overall [30], 7601 patients were followed for a median time of 37.7 months; the results show that candesartan (32 mg/day) reduced the relative risk of developing diabetes by 22% compared to placebo. In CHARM-Preserved [31], patients with heart failure of class II-IV and with an ejection fraction less than 50% were followed for a median time of 36.6 months. Candesartan (32 mg/day) reduced the relative risk of developing diabetes by 39% compared to placebo.

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Several other large-scale intervention trials are ongoing, such as those involving valsartan: VALUE, VALHEFT, VALIANT, and NAVIGATOR [33–35]. NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) is the largest diabetes prevention study ever. So far, 9150 individuals with impaired glucose tolerance have been included at one of 600 to 800 centers in 40 countries. This study will show whether restoration of the early insulin response (with nateglinide) and/or blockade of the RAS and improvement of insulin sensitivity (with valsartan) can prevent the transition from impaired glucose tolerance to type 2 diabetes, and whether this influences the incidence of cardiovascular disease [33].

**Statins**

WOSCOPS, a primary prevention study, examined post hoc whether there was any connection between inflammatory activity and the risk of developing type 2 diabetes, and whether treatment with pravastatin could reduce the risk [36]. The results show that pravastatin (40 mg/day) reduced the relative risk of developing diabetes during the 4.9-year duration of the study by 30% compared to placebo.

The prospective PRINCE study [37] and the retrospective CARE study [38] showed that pravastatin reduces CRP levels (detectable within 12 weeks) and that this occurs independently of reductions in LDL levels. Similar effects have been reported in other studies [39–41]. If one examines the CARE study in detail it becomes apparent that pravastatin in fact only reduced the risk of cardiovascular mortality in those patients who had elevated levels of CRP, and not in those with low CRP levels [38]. It is tempting to speculate that the antiinflammatory properties of pravastatin explains why the drug reduced the risk of incident diabetes in WOSCOPS.

There appear to be important differences between the statins in this regard, as pravastatin is in a class of its own in terms of preventing diabetes. To the best of our knowledge, no other statin has shown any antidiabetogenic effect. For instance, no such effect was reported in HPS (the Heart Protection Study), where simvastatin was used [42]. Suggestively, simvastatin differs in several respects from other statins, with the possible exception of rosvuastatin, for which there are as yet no data on mortality. Pravastatin is not metabolized by hepatic CYP-450 enzymes, shows very little binding to proteins, and is markedly hydrophilic. Whether these special characteristics or other attributes underlie pravastatin’s antidiabetogenic effect remains to be shown. The results from WOSCOPS must be independently confirmed by other studies; until then, the evidence for an antidiabetogenic effect of pravastatin must be considered weaker than the evidence for such effects of ACE inhibitors and angiotensin receptor antagonists. Other mechanisms are conceivable, for instance, direct effects on the endocrine pancreas. In vitro studies have shown that lipophilic statins (simvastatin) inhibit glucose-stimulated insulin secretion by blocking voltage-gated L-type Ca$^{2+}$ channels in insulin-secreting beta cells, whereas...
pravastatin has no such adverse effect [43]. Furthermore, pravastatin can prevent inflammation and rejection of transplanted Langerhans islets [44].

It should be noted that, besides pharmacological treatment, simple life-style changes (decrease in body weight, increased physical activity) also strongly decrease low-grade inflammation.

**Pathophysiological correlates**

The new class of insulin-sensitizing agents (glitazones) – which have been introduced against type 2 diabetes and insulin resistance – exert their effects by activating PPAR-\(\gamma\) (peroxisome proliferator activator receptor \(\gamma\)) in the cell nucleus, where it then influences a range of transcription factors [45–47]. Glitazones ameliorate endothelial dysfunction in patients with diabetes, and have also been shown to reduce the levels of CRP, leptin, PAI-1, TNF-\(\gamma\) and other inflammatory markers in serum [5,45–47]. The production of reactive oxygen species is also reduced. One newly discovered and potentially important effect of glitazones is inhibition of the enzyme 11\(\beta\)-hydroxysteroid dehydrogenase type 1, which metabolizes cortisone [48,49]. The effect of glitazones on CRP levels, detectable within a week, amounts to a 30% reduction; for comparison, the corresponding effect of statins is only 14% [4,5]. Data on other antidiabetic agents are scarce, but it appears that metformin and certain types of sulfonylurea drugs may have similar anti-inflammatory activity [4,5,50].

It has long been debated whether insulin causes atherogenesis; this has no doubt contributed to reluctance to prescribe insulin to patients with early type 2 diabetes. However, the evidence for a causal relation emanates mainly from \textit{in vitro} studies where extremely high – physiologically irrelevant – concentrations of insulin have been shown to induce cell proliferation and potentially also lead to atherogenesis [4,5]. In addition, epidemiological studies have revealed co-variation between hyperinsulinemia and cardiovascular risk [4,5]. In all likelihood it is the other way around, that the insulin resistance \textit{per se} – by way of production of pro-inflammatory cytokines – induces atherogenesis and that the hyperinsulinemia should be seen as the body’s compensatory attempts to suppress the inflammation and overcome the insulin resistance [4,5]. In other words, insulin would be anti-inflammatory and thus also antiatherogenic.

It has recently been demonstrated in human subjects that infusion of low doses of insulin (2 E/h) in obese individuals reduces the production of reactive oxygen species in leukocytes (which increases the bioavailability of anti-inflammatory nitric oxide (NO)), as well as reduced the levels of CRP and other inflammatory markers in serum [4,5]. The effect corresponded to that of an i.v. dose of 100 mg of hydrocortisone. It appeared rapidly, within two hours of the infusion, and also receded quickly [4,5]. In addition, data from \textit{in vivo} studies show that insulin acts via NO-mediated mechanisms to suppress synthesis of pro-inflammatory substances in endothelial cells from human aorta [4,5]. Thus, there is good reason to consider insulin as an anti-inflammatory hormone. A vicious circle can also develop: if insulin sensitivity decreases in organs such as skeletal muscle, adipose tissue and liver, this leads to increased inflammatory activity, which in turn leads to further reductions of insulin sensitivity. Moreover, glucose had several pro-inflammatory effects. Glucose increases synthesis of reactive oxygen species and accentuates several inflammatory parameters \textit{in vitro} [4,5]. Likewise, under hyperglycemic clamp conditions, if endogenous insulin secretion is suppressed with somatostatin, the synthesis of IL-6 and TNF-\(\alpha\) increase [4,5].

In concordance with this, hypoglycemic effects have been reported for salicylates and anti-inflammatory non-steroid anti-inflammatory drugs (NSAIDs), which inhibit the enzyme cyclooxygenase (COX) [51–54]. Certain COX inhibitors are able not only to enhance glucose-induced insulin release in humans, but also to improve glucose tolerance and glucose-induced insulin release in patients with type 2 diabetes [51–53]. That salicylates in doses of about a gram can cause hypoglycemia has been known since the 1870s. Salicylates have also been reported to enhance the effect of insulin [4,5]. High doses also inhibit the enzyme IkB-kinase B, which is involved in the immune response, and reduce fat-induced insulin resistance in muscle [4,5]. In humans, this results in a 25% decrease in fasting glucose and reduction of the levels of CRP (15%), cholesterol (15%) and triglycerides (50%) and reduces insulin clearance (30%) [4,5]. In parallel, hepatic glucose production and insulin-sensitive glucose uptake in the periphery increase by about 20% [4,5].

Further experimental support for this theory comes from experiments with transgenic animals, where \textit{overexpression} of IkB-kinase B leads to reduced insulin sensitivity – an effect that could be counteracted with salicylates [55]. If instead IkB-kinase B was \textit{underexpressed}, the animals were protected against developing of insulin resistance when given a high-fat diet [55]. IkB-kinase B thus appears to be a promising target for drug development. In summary, these data give further support to the notion that inflammation plays a pivotal role in the pathogenesis of type 2 diabetes and insulin resistance.

One simple explanation for the improvement in insulin sensitivity could be that blood flow through the microvasculature to insulin-sensitive tissues (e.g. skeletal muscle) increases after treatment with vasoactive substances, thus allowing more insulin to reach metabolically active tissue. However, it has been shown that irbesartan [56] and other drugs that block the renin–angiotensin system [57–63] reduce the levels of inflammatory markers in serum of patients with diabetes. Moreover, angiotensin II stimulates IL-2 production in macrophages and smooth muscle cells; the peptide also increases hepatic IL-6 production in parallel with increased insulin resistance [4,5]. Angiotensin II also inhibits adipocyte differentiation, and
there is an inverse correlation between insulin sensitivity and expression of angiotensin-II-producing enzymes in adipose tissue [64]. The mechanistic interpretation is that blockade of the RAS by ACE inhibitors or angiotensin receptor antagonists reduces the risk of diabeticogenesis by stimulating proliferation and differentiation of adipocytes [64]. In this way, ectopic fat storage (e.g. in liver, skeletal muscle and pancreas), which is associated with insulin resistance, would be prevented. Thus this mechanism, if it can be confirmed, is in good agreement with the manner in which glitazones reduce insulin resistance in patients with type 2 diabetes [45–47].

Clinical perspectives

In recent years, several studies have been published that implicate subclinical chronic inflammation as an important pathogenetic factor in the development of insulin resistance and type 2 diabetes. This opens new perspectives for diagnosis and treatment of early insulin resistance and incipient glucose intolerance. More specific and sensitive biomarkers should be identified, which may predict early disturbances in insulin sensitivity and cardiovascular risk. The inflammatory signalling pathways need to be explored in greater detail, and may form the basis of drugable targets against the epidemic of insulin resistance and atherosclerosis.

Acknowledgements


References


33. Calif RR, Holman R. People at increased risk of cardiovascular disease screened for the NAVIGATOR trial frequently have undiagnosed diabetes or impaired glucose tolerance. J Am Coll Cardiol 2003; 41 (6 Suppl. 2): 530–531.
